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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,758	LIANG ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,30-33,35-39,41 and 43-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,30-33,35-39,41 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed November 14, 2005. Claims 1-3, 5-8, 21-25, 27-39, 41 and 43-46 were previously pending. Applicants amended claim 30 and cancelled claims 21-25, 27-29, 34 and 46. Claims 1-3, 5-8, 30-33, 35-39, 41 and 43-45 are pending and will be examined.

2. Applicants are advised that the instant amendment is not in compliance with the 37 C.F.R. 1.121 rule regarding amendments in that claim 35 is indicated as being currently amended but there is no indication of what changes the amendment introduced. For the sake of advancing prosecution the amendment is going to be considered, but Applicants should correct claim status identifiers in the response.

3. Applicants' claim cancellations and arguments overcame the following rejections: rejections of claims 1, 2, 5, 6, 21, 22, 27-34 and 46 under 35 U.S.C. 102(b) as anticipated by Shi et al.; rejection of claims 3, 23 and 35 under 35 U.S.C. 103(a) over Shi et al. and Felgner et al.; rejection of claims 7, 8, 24, 25, 36 and 37 under 35 U.S.C. 103(a) over Shi et al. and Uhlman et al.; rejection of claims 38, 39, 41 and 43 under 35 U.S.C. 103(a) over Shi et al. and Mullis et al; rejection of claims 44 and 45 under 35 U.S.C. 103(a) over Shi et al., Mullis et al. and Uhlman et al.

4. Applicants' arguments are moot in view of new grounds for rejection. This office action is made non-final because of new grounds for rejection.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Before proceeding with the rejections, it is noted that the term "nucleic acid sequence that confers function" is interpreted in its broadest meaning, i.e., any function that can be assigned to a nucleic acid. Further, since there is no requirement in the claims that the steps to performed in a sequential manner, performing all of the steps at the same time anticipates the claims in view of the preamble containing the phrase "comprising".

7. Claims 1, 2, 5, 6 and 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Prodromou et al. (Protein Engineering, vol. 5, pp. 827-829, 1992; cited in a previous office action).

Regarding claim 1, Prodromou et al. teach a method for amplifying a transcriptionally-active polynucleotide, comprising:

performing a first PCR-amplification step to amplify a first target fragment of DNA with a first primer pair, wherein the first primer pair, upon such amplification, adds to first and second ends of the first fragment predetermined first and second regions of complementarity, to form a second DNA fragment having said first region of complementarity at a first end and a second region of complementarity at a second end of said second DNA fragment (Prodromou et al. teach synthesis of human lysozyme gene by recursive PCR from ten oligonucleotide fragments. The oligonucleotides were 54-86 bases long and contained overlaps of 17-20 bp in length (page 828). Therefore, each of the fragments served as a primer or target for the neighboring fragments (Fig. 1). Therefore, at any point during the amplification reaction, each fragment, except for fragments 1, 2, 9 and 10, is contacted with two primers, both of which contain regions of complementarity to which the next two primers anneal. For example, in an idealized situation (because in reality all of the intermediates are present at once), a fragment synthesized from fragments 3-8 is contacted with fragments 2 and 9, which have regions of complementarity to fragments 1 and 10.);

providing a promoter-containing sequence and a terminator-containing sequence, said promoter-containing sequence further including a region complementary to said first region of complementarity, and said terminator-containing sequence further including a region complementary to said second region of complementarity, wherein both said promoter-containing sequence and said terminator-containing sequence include an internal nucleotide capable of forming an A-T base pair immediately adjacent to said region of complementarity (Prodromou et al. teach providing fragments 1 and 10, with fragment 1 containing the promoter sequence and fragment 10 containing the terminator sequence (Fig. 2, page 828). Both the first fragment and the tenth fragment contain nucleotides capable of forming an A-T base pair immediately adjacent to the regions of complementarity; Fig. 2.);

joining said promoter-containing sequence to said first end of said second DNA fragment and said terminator-containing sequence to said second end of said second DNA fragment to form said third DNA fragment (Prodromou et al. teach PCR amplifying the fragments, which means, for example amplifying target fragment 2-9 with fragments 1 and 10, joining the promoter and terminator-containing fragments to fragment 2-9 (Fig. 1; page 829, second paragraph; Fig. 3).); and

PCR-amplifying said third DNA fragment (Prodromou et al. teach PCR amplifying the fragments, which includes amplification of the whole gene (page 829, second paragraph). Since primers 1 and 10 were present in large excess over the rest of the fragments, the final amplification was performed with just these primers).

Regarding claim 2, Prodromou et al. teach PCR amplifying the fragments, which means, for example amplifying target fragment 2-9 with fragments 1 and 10, joining the promoter and terminator-containing fragments to fragment 2-9 (Fig. 1; page 829, second paragraph; Fig. 3).

Regarding claims 5 and 6, Prodromou et al. teach Vent or Taq polymerase (page 829, first and second paragraphs).

Regarding claim 30, Prodromou et al. teach a reaction mixture (= system for adding a nucleic acid fragment that confers function to a polynucleotide sequence), comprising:

an extension primer pair, each primer of which comprises a region of complementarity to a strand of the polynucleotide target sequence and a predetermined extension region (Prodromou et al. teach a reaction mixture that contains the oligonucleotides with sequences complementary to the target sequence and extension regions , such as oligonucleotides 2-9 (extension primer pairs) (Fig. 1, page 829, second paragraph); and

a 5' biological function conferring nucleic acid fragment and a 3' biological function conferring nucleic acid fragment, each fragment of which comprises a region of complementarity to one of the extension regions, and a biological function conferring polynucleotide sequence that confers biological function, wherein the extension primer pairs are adapted to add the extension regions to a target sequence upon a first PCR procedure, and the function conferring nucleic acid pairs are adapted to add the functional polynucleotide sequences to the target sequence upon a second PCR procedure, wherein the 5' biological function conferring nucleic acid fragments comprises a promoter and the 3' biological function conferring nucleic acid fragments comprises a terminator (Prodromou et al. teach a reaction mixture that contains oligonucleotides 1 and 10, which contain a promoter and a terminator, respectively (= biological function conferring polynucleotides) (Fig. 2). The limitation following the first "wherein" clause is an intended use limitation, therefore they do not impose structural limitation upon the claimed product.).

Regarding claims 31-33, Prodromou et al. teach a reaction mixture comprising a Vent polymerase (page 829, second paragraph) and teach using Taq polymerase (page 829, third paragraph).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 3 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prodromou et al. (Protein Engineering, vol. 5, pp. 827-829, 1992; cited in a previous office action) and Felgner et al. (U. S. Patent No. 6,165,720; cited in the IDS and in the previous office action).

A) The teachings of Prodromou et al. are described above. Prodromou et al. teach addition of promoter and terminator to a nucleic acid fragment, but do not teach insertion of the PNA-binding domain.

B) Regarding claims 3 and 35, Felgner et al. teach construction of nucleic acid vectors (or plasmids) containing PNA-binding sites (col. 12, lines 46-67; col. 13, lines 1-26; col. 26, lines 64-67; col. 27, 28; Fig. 8). The PNA-binding sites confer the following properties onto the plasmids: increased transfection efficiency, nuclear localization, transcription activation, endosomal lytic activity and immunostimulatory activity (col. 6, lines 29-47).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added PNA-binding sites of Felgner et al. to transcriptionally-active nucleic acids of Prodromou et al. The motivation to do so, provided by Felgner et al., would have been that

binding of PNA clamps to PNA-binding sites provided nuclease resistance to DNA duplexes (col. 6, lines 48-54).

10. Claims 7, 8, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prodromou et al. (Protein Engineering, vol. 5, pp. 827-829, 1992; cited in a previous office action) and Uhlman et al. (U. S. Patent No. 6,063,571; cited in the previous office action).

A) The teachings of Prodromou et al. are described above. Prodromou et al. teach addition of promoter and terminator to a nucleic acid fragment, but do not teach PNA molecules which confer nuclease resistance.

C) Regarding claims 7, 8, 36 and 37, Uhlman et al. teach amplification of nucleic acids with DNA/PNA primers, which contain a PNA moiety at the 5' end of the primer. Such primers can be used with temperature-stable polymerases (col. 2, lines 30-49; col. 5, lines 8-46). Uhlman et al. teach that nucleic acid fragments amplified with DNA/PNA primers are resistant to exonucleases (col. 1, lines 32-39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the DNA/PNA primers of Uhlman et al. in the amplification method of Prodromou et al. The motivation to do so, provided by Uhlman et al., would have been that PNA confers nuclease resistance to a DNA attached to it (col. 1, lines 32-39).

11. Claims 38-39, 41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prodromou et al. (Protein Engineering, vol. 5, pp. 827-829, 1992; cited in a previous office action) and Mullis et al. (U.S. Patent No. 4,965,188; cited in the previous office action).

A) Regarding claim 38, Prodromou et al. teach a method of adding a nucleic acid sequence that confers function to a polynucleotide target sequence, the method comprising:

contacting first and second nucleic acid fragments with a polynucleotide target sequence, wherein the first nucleic acid fragment comprises a first region of complementarity to a portion of the polynucleotide target sequence and a first extension region, and the second nucleic acid fragment comprises a second region of complementarity to a portion of the polynucleotide target sequence and a second extension region (Prodromou et al. teach synthesis of human lysozyme gene by recursive PCR from ten oligonucleotide fragments. The oligonucleotides were 54-86 bases long and contained overlaps of 17-20 bp in length (page 828). Therefore, each of the fragments served as a primer or target for the neighboring fragments (Fig. 1). The 5'-most fragment contained the promoter sequence and the 3'-most fragment contained the terminator sequence (Fig. 2, page 828). Therefore, at any point during the amplification reaction, each fragment, except for fragments 1, 2, 9 and 10, is contacted sequentially with two sets of primers, both of which contain regions complementary to the fragment and extension regions, to which the next two primers anneal. For example, in an idealized situation (because in reality all of the intermediates are present at once), a fragment synthesized from fragments 3-8 is contacted with fragments 2 and 9, which have regions complementary to fragments 3 and 8, and extension regions.);

PCR amplifying the first and second nucleic acid fragments and the polynucleotide target sequence, to form an intermediate nucleic acid fragment that comprises the polynucleotide target sequence flanked by the first and second extension regions (Prodromou et al. teach PCR amplifying the fragments, which means, for example amplifying target fragment 3-8 with fragments 2 and 9 (Fig. 1; page 829, second paragraph).);

contacting the intermediate nucleic acid fragment with a third and fourth nucleic acid fragments that respectively comprises a region complementary to the first and second extension regions, wherein one or both of the third and fourth nucleic acid fragments further comprise at least

one nucleic acid region that confers function (Prodromou et al. teach contacting the resulting product, fragment 2-9 with fragments 1 and 10, with fragment 1 having a region complementary to the extension region of fragment 2 and comprising a promoter sequence, and fragment 10 having a region complementary to the extension region of fragment 9 and comprising a terminator sequence.); and

PCR amplifying the intermediate nucleic acid fragment with the third and fourth nucleic acid fragments to form a product nucleic acid fragment that comprises one or more functional nucleic acid regions joined to the polynucleotide target sequence (Prodromou et al. teach PCR amplifying the fragments, which means, for example amplifying target fragment 2-9 with fragments 1 and 10, producing a transcriptionaly active product (Fig. 1; page 829, second paragraph; Fig. 3).).

Regarding claim 39, Prodromou et al. teach a transcriptional functional region being a promoter (on oligonucleotide 1) or a terminator (on oligonucleotide 10) and addition of both to the final gene sequence (Fig. 2).

Regarding claim 43, Prodromou et al. teach amplification using a Vent or Taq polymerase (page 829, first and second paragraphs).

B) Prodromou et al. do not teach amplification of more than one target nucleic acid or separate amplification of different targets.

C) Regarding claim 38, Mullis et al. teach that in polymerase chain reaction more than one target nucleic acid can be amplified using primers specific for each target (col. 3, lines 1-67; col. 4, lines 1-5; col. 13, lines 20-30). The primers may have sequences non-complementary to the target attached at the 5' end of the primers, and the non-complementary sequences may contain promoters, linkers, coding sequences, etc. (col. 6, lines 44-53; col. 19, lines 60-67; col. 20, lines 1-6).

Regarding claim 41, Mullis et al. teach amplification of different target nucleic acids in separate tubes (col. 34, lines 57).

It would have been *prima facie* obvious to one of ordinary skill in the art to have amplified more than one target nucleic acid according to Mullis et al. in the method of gene synthesis of Prodromou et al. The motivation to do so, provided by Mullis et al., was that multiple nucleic acids are produced in large quantities (col. 9, lines 36-41).

12. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prodromou et al. (Protein Engineering, vol. 5, pp. 827-829, 1992; cited in a previous office action) and Uhlman et al. (U. S. Patent No. 6,063,571; cited in the previous office action).

Regarding claim 44, Prodromou et al. teach a method of adding a nucleic acid sequence that confers function to a polynucleotide target sequence, the method comprising:

contacting first and second nucleic acid fragments with a polynucleotide target sequence, wherein the first nucleic acid fragment comprises a first region of complementarity to a portion of the polynucleotide target sequence and a first extension region, and the second nucleic acid fragment comprises a second region of complementarity to a portion of the polynucleotide target sequence and a second extension region (Prodromou et al. teach synthesis of human lysozyme gene by recursive PCR from ten oligonucleotide fragments. The oligonucleotides were 54-86 bases long and contained overlaps of 17-20 bp in length (page 828). Therefore, each of the fragments served as a primer or target for the neighboring fragments (Fig. 1). The 5'-most fragment contained the promoter sequence and the 3'-most fragment contained the terminator sequence (Fig. 2, page 828). Therefore, at any point during the amplification reaction, each fragment, except for fragments 1, 2, 9 and 10, is contacted sequentially with two sets of primers, both of which contain regions complementary to the fragment and extension regions, to which the next two primers anneal. For

example, in an idealized situation (because in reality all of the intermediates are present at once), a fragment synthesized from fragments 3-8 is contacted with fragments 2 and 9, which have regions complementary to fragments 3 and 8, and extension regions.);

PCR amplifying the first and second nucleic acid fragments and the polynucleotide target sequence, to form an intermediate nucleic acid fragment that comprises the polynucleotide target sequence flanked by the first and second extension regions (Prodromou et al. teach PCR amplifying the fragments, which means, for example amplifying target fragment 3-8 with fragments 2 and 9 (Fig. 1; page 829, second paragraph).);

contacting the intermediate nucleic acid fragment with a third and fourth nucleic acid fragments that respectively comprises a region complementary to the first and second extension regions, wherein one or both of the third and fourth nucleic acid fragments further comprise at least one nucleic acid region that confers function (Prodromou et al. teach contacting the resulting product, fragment 2-9 with fragments 1 and 10, with fragment 1 having a region complementary to the extension region of fragment 2 and comprising a promoter sequence, and fragment 10 having a region complementary to the extension region of fragment 9 and comprising a terminator sequence.); and

PCR amplifying the intermediate nucleic acid fragment with the third and fourth nucleic acid fragments to form a product nucleic acid fragment that comprises one or more functional nucleic acid regions joined to the polynucleotide target sequence (Prodromou et al. teach PCR amplifying the fragments, which means, for example amplifying target fragment 2-9 with fragments 1 and 10, producing a transcriptionaly active product (Fig. 1; page 829, second paragraph; Fig. 3).).

B) Prodromou et al. teach addition of promoter and terminator to a nucleic acid fragment, but do not teach PNA molecules which confer nuclease resistance.

C) Regarding claims 44 and 45, Uhlman et al. teach amplification of nucleic acids with DNA/PNA primers, which contain a PNA moiety at the 5' end of the primer. Such primers can be used with temperature-stable polymerases (col. 2, lines 30-49; col. 5, lines 8-46). Uhlman et al. teach that nucleic acid fragments amplified with DNA/PNA primers are resistant to exonucleases (col. 1, lines 32-39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the DNA/PNA primers of Uhlman et al. in the amplification method of Prodromou et al. The motivation to do so, provided by Uhlman et al., would have been that PNA confers nuclease resistance to a DNA attached to it (col. 1, lines 32-39).

13. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TERESA STRZELECKA
PATENT EXAMINER
Teresa Strzelecka
1/20/06